with 58 g (270 mmol) of ethyl bromide in 40 mL of acetonitrile in an autoclave at 100 °C for 2 days. The solvent was evaporated, and the residue was washed with ether and ethyl acetate successively. Recrystallization from acetonitrile yielded 580 mg (6%) of **2b** hydrate: mp 211 °C; $[\alpha]^{25}_D$ +55.6° (*c* 2.2, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 0.8–3.0 (m, 20 H), 4.0–4.9 (m, 8 H), 7.3–7.7 (m, 10 H), 10.0 (br, 2 H). Anal. Calcd for C$_{27}$H$_{38}$NBr·H$_2$O (474.5): C, 68.34; H, 8.43; N, 2.95. Found: C, 64.18; H, 8.15; N, 2.92.

Phase Transfer Catalytic Ether Formation. To a mixture of 10 g of 50% NaOH, 40 mL of petroleum ether (boiling range 30–60 °C), 4.88 g (40 mmol) of 1-phenylethanol, and 0.4 mmol of catalyst was added 2.52 g (20 mmol) of Me$_2$SO$_4$ (40 mmol in the case of optically active compound). Thereafter a slight exothermic reaction occurred. The mixture was stirred at room temperature for 1 h, 8 mL of 50% aqueous ammonia was added, and the mixture was stirred again for 5 min. The phases were separated, and the organic layer was washed three times with 20-mL portions of H$_2$O and dried over Na$_2$SO$_4$. Removal of the solvent and fractional distillation gave the ether, bp 68 °C/16 Torr. Yields with 1, **2a**, **2b** as catalysts: 74, 60, or 74%, respectively, $[\alpha]^{25}_D$ 0.0° (*c* 13.6, MeCN). Yield with optically active alcohol and tetrabutylammonium chloride as catalyst: 82%, $[\alpha]^{26}_D$ −114.0° (neat) (in solution, see text).
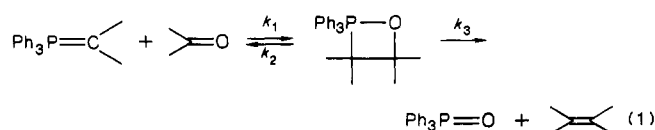

Mechanistic Study of the Wittig Reaction of Benzophenone with a Nonstabilized Ylide

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The Wittig reaction is one of the most important reactions in organic synthesis, and extensive studies have been performed to elucidate the mechanism.[1] In spite of the amount of investigation, however, some important points still remain unclear, e.g., the origin of cis preference in reactions of nonstabilized ylides, the intermediacy of betaine, and the nature of the rate-determining step of the multistep reaction. Reactions of nonstabilized ylides with simple aldehydes or ketones have been shown by ^{31}P NMR to go through oxaphosphetanes as an only detectable intermediate.[2,3] Thus, ethylidenetriphenylphosphorane reacted with cyclohexanone at −78 °C in THF to give a sharp signal, attributable to oxaphosphetane, at 66.5 ppm relative to external 85% phosphoric acid. At higher temperature above −15 °C, the oxaphosphetane was converted into triphenylphosphine oxide.[2] This finding as well as others was interpreted in terms of the scheme shown in eq 1; oxaphosphetane forms rapidly and then decomposes to phosphine oxide and alkene in a slow step. In the

$$Ph_3P{=}C{<} + {>}{=}O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \begin{array}{c} Ph_3P{-}O \\ | \quad | \\ | \quad | \end{array} \xrightarrow{k_3}$$

$$Ph_3P{=}O + {>}{<} \qquad (1)$$

reaction of benzaldehyde and *n*-butylidenetriphenylphosphorane, both *cis*- and *trans*-oxaphosphetanes have been observed and the rates of decomposition of these intermediates have been determined by the ^{31}P NMR method.[3] The intermediacy of the betaine species was questioned for the reactions of nonstabilized ylides.

However, studies by use of ^{31}P NMR are so far limited to the reaction systems in which the oxaphosphetane is far more stable than the reactants (ylide + aldehyde or ketone) and therefore only the decomposition of the oxaphosphetane could be followed kinetically. In spite of that, the oxaphosphetane formation step was suggested to be crucial in determining the stereochemistry of the overall reaction. In the present paper, we report the results of an NMR study for the reaction of benzophenone with a nonstabilized ylide, wherein both formation and decomposition of oxaphosphetane could be monitored for the first time. Substituent and kinetic isotope effect (KIE) experiments were also carried out, which are known to be useful in obtaining information on the rate-determining step of reactions.

A THF solution of isopropylidenetriphenylphosphorane (0.1 M), prepared from isopropyltriphenylphosphonium iodide and sodium hexamethyldisilazide, was placed in a flame-dried NMR tube and cooled by liquid N$_2$. To this was added a benzophenone solution, and the tube was sealed.[4] The THF solution containing ylide (0.052 M), benzophenone (0.075 M), and THF-d_8 (8.3% v/v, internal D-lock) was then allowed to react at 0 °C and examined at 40.5 MHz FT-NMR with proton noise decoupling. Figure 1 shows the time dependence of the spectrum. The signal at −55.3 ppm was assigned to oxaphosphetane from analogy with the literature values.[2,3] The other five signals were assigned by using authentic samples and/or by ^{1}H NMR analysis to those of triphenylphosphine (external standard, adjusted to −5.5 ppm), ylide (10.8), triphenylphosphine oxide (27.3), isopropyltriphenylphosphonium iodide (33.1), and isopropyldiphenylphosphine oxide (36.9). No peak attributable to betaine was observed, although a very short-lived betaine may escape detection.

From the results in Figure 1 the kinetic analysis was made and illustrated in Figure 2. The variation of oxaphosphetane in Figure 2 suggests that the reaction proceeds consecutively and that the olefin-formation step is not a single rate-determining step in sharp contrast to the reaction of cyclohexanone.[2] Thus, the reaction profile for benzophenone is quite different from that for cyclohexane or various aldehydes. By assuming the reaction scheme of eq 1, we carried out computer simulation of the plots with k_1, k_2, and k_3 being adjustable parameters. As Figure 2 shows, theoretical lines fit nicely with the experimental points. A series of parameter sets were found to reproduce the observed data. The conclusions obtained from the simulation are (1) k_3 is in the order of 7×10^{-4} s^{-1}, (2) k_1

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(4) Olah et al. have reported that the reaction of isopropylidenetriphenylphosphorane, prepared with *n*-BuLi as a base, with benzophenone gave benzhydrol in addition to the expected alkene product in toluene. The formation of the reduced product was ascribed to an electron-transfer mechanism. We repeated the experiments and indeed obtained benzhydrol although in a lower yield. However, when PhLi or sodium hexamethyldisilazide was used in place of *n*-BuLi, the reaction gave the expected alkene exclusively either in toluene, ether, or THF, and the material balance in these reactions was excellent: Olah, G. A.; Krishnamurthy, V. V. *J. Am. Chem. Soc.* **1982**, *104*, 3987.
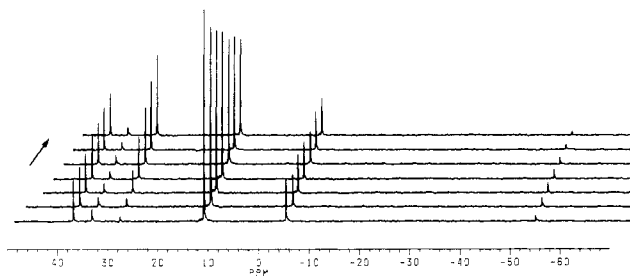
Figure 1. ^{31}P NMR stacked plots for the reaction of iso-propylidenetriphenylphosphorane with benzophenone in THF at 0 °C. Time points (from bottom to top) are 13.5, 32.5, 59.0, 97.0, 135.0, 173.0, and 211.0 min, respectively.
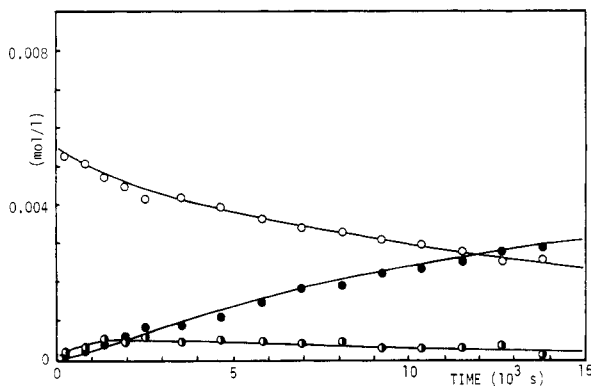

Figure 2. Rate profile for the reaction of isopropylidenetriphenylphosphorane with benzophenone at 0 °C: (O) ylide; (◑) oxaphosphetane; (●) triphenylphosphine oxide.

and k_2 can be varied simultaneously in the same direction but k_1 is always larger than k_2, (3) in all cases k_1 is larger than k_3 while k_2 can be smaller or larger than k_3, and (4) the best fit (shown in Figure 2) was obtained with the following rate constants: $k_1 = 1.3 \times 10^{-3}$ L mol^{-1} s^{-1}, $k_2 = 4.0 \times 10^{-4}$ s^{-1}, and $k_3 = 7.0 \times 10^{-4}$ s^{-1}.

The carbonyl carbon KIE and substituent effects were determined by the methods described previously.[5] The observed KIE was 1.053 ± 0.002 in THF (Li salt free) at 0.0 °C. This clearly indicates that the bonding of the carbonyl carbon is changing at the rate-determining transition state of the Wittig reaction. Thus, the possibility of a rate-determining electron-transfer mechanism can be eliminated; the carbonyl carbon KIE is expected to be unity for a reaction in which an initial electron-transfer step is rate-determining.[5] Substituent effects were determined by the competition experiments,[5] and were plotted in Figure 3 against the standard σ constants. Since reliable σ constants of ortho substituents were not available, the log (k_X/k_H) values for the ortho derivatives were plotted against the corresponding para-substituent constants and are indicated by closed circles. The ρ value was calculated from the points of the meta- and para-substituted derivatives. Two facts are apparent from Figure 3: a considerable ρ value[6] and substantial steric rate retardation for the ortho-substituted derivatives compared with
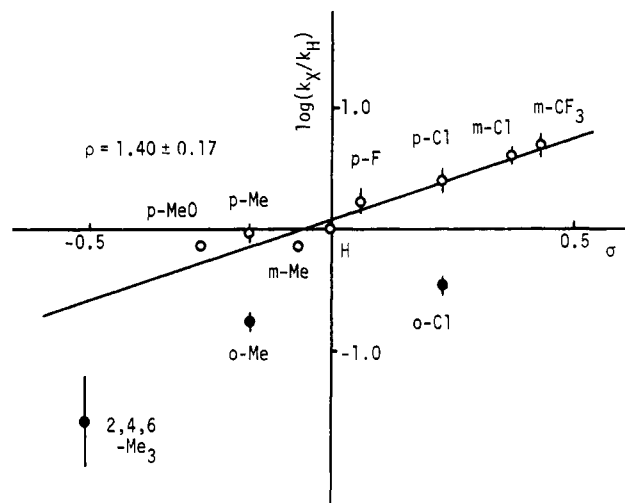
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(6) Larger ρ values have been reported for the reactions of substituted benzaldehydes with stable or metastable ylides. Speziale, A. J.; Bissing, D. E. *J. Am. Chem. Soc.* **1963**, *85*, 3878. Isaacs, N. S.; Abed, O. H. *Tetrahedron Lett.* **1986**, *27*, 995. Donxia, L.; Dexian, W.; Yaozhong, L.; Huaming, Z. *Tetrahedron* **1986**, *42*, 4161.

Figure 3. Variations of reactivity with σ values for the reactions of substituted benzophenones with isopropylidenetriphenylphosphorane. Closed circles refer ortho substituents.

the corresponding para-substituted derivatives. The results of the KIE and substituent effect experiments are similar to those of carbonyl additions such as NaBH$_4$ reduction,[7] AlH$_3$ reduction,[8] and the Grignard reaction[9] of benzophenone.

The present results are most consistent with the mechanism, in which the rate-determining step is the direct formation of oxaphosphetane, although the decomposition of the oxaphosphetane may also be rate-limiting. The formation and the decomposition of oxaphosphetane may have similar transition-state characteristics as far as the carbonyl carbon of the ketone is concerned, and thus both steps may give similar KIE and substituent effects. Further study is required to clarify this point.

Experimental Section

Materials. THF was dried over LiAlH$_4$ and distilled before use. Isopropyltriphenylphosphonium iodide was obtained by the reaction of isopropyl iodide and triphenylphosphine and recrystallized from ethanol–diethyl ether. Isopropylidenetriphenylphosphorane was prepared by treating isopropyltriphenylphosphonium iodide with 1.2 molar equiv of sodium hexamethyldisilazide in THF at room temperature. Substituted benzophenones were synthesized by either the Friedel–Crafts reactions of substituted benzoyl chlorides with benzene (*m*-Cl and *o*-Me) or the Grignard reaction of arylmagnesium bromide with benzaldehyde followed by the oxidation of the resulting benzhydrol with KMnO$_4$ (*m*-CF$_3$). 2,4,6-Trimethylbenzophenone was synthesized by the reaction of benzoyl chloride with 1,3,5-trimethylbenzene. Other substituted benzophenones were commercially available and used after appropriate purification procedures. Benzophenone-*carbonyl*-^{14}C was prepared by the Friedel–Crafts benzoylation of benzene with benzoyl chloride-^{14}C, which was obtained by chlorination of benzoic acid-7-^{14}C (NEN) with thionyl chloride.

NMR Spectroscopic Measurements and Rate Studies. NMR spectra were recorded on a JEOL-JNM-FX100 spectrometer operating at 40.5 MHz for phosphorus. For ^{31}P measurements, a 7-μs pulse, equivalent to a 45° flip angle, with a 30-s recycle time was used. The conditions were chosen to ensure that the relaxation times of the species (determined by the T_1 null

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Table I. Kinetic Isotope Effect in the Wittig Reaction of Benzophenone-*carbonyl*-^{14}C with Isopropylidenetriphenylphosphorane in THF at 0 °C

no.	fraction of reaction	molar radioactivity,[a] mCi/mol	$^{12}k/^{14}k$
1	0	0.4831 ± 0.0009	
2	0.189	0.4893 ± 0.0006	1.057
3	0.330	0.4933 ± 0.0011	1.051
4	0.447	0.4986 ± 0.0005	1.053
5	0.561	0.5048 ● 0.0007	1.054
6	0.667	0.5103 ± 0.0003	1.050

av 1.053 ± 0.002

[a] Errors are the standard deviations from the averages of multiple radioactivity measurements.

method) were sufficiently short for accurate integrals. The effect of NOE on the relative intensity of the signals was determined at –60 °C and calibrated. We estimated that the reproducibility of the intensity was ca. 5%, and the results from the kinetic treatment should be taken qualitatively.[10] Kinetic analysis was made on the basis of the reaction scheme shown in eq 1. Three differential equations were obtained in a usual manner. From these the following three equations were assumed for a very small Δt:

$$A_{t+\Delta t} = A_t + (-k_1 A_t B_t + k_2 C_t)\Delta t$$

$$C_{t+\Delta t} = C_t + (k_1 A_t B_t - k_2 C_t - k_3 C_t)\Delta t$$

$$D_{t+\Delta t} = D_t + k_3 C_t \Delta t$$

Here, A_t, B_t, C_t, and D_t refer to the concentration of ylide, ketone, oxaphosphetane, and triphenylphosphine oxide at t, respectively. Starting from the initial conditions of $t = 0$, three quantitites, $A_{t+\Delta t}$, $C_{t+\Delta t}$, and $D_{t+\Delta t}$, were calculated step by step for a small increment of Δt.

Competition Experiments. A pair of ketones (normally the parent and a substituted benzophenone, 0.14 mmol each) and dibenzyl ether (0.05 mmol, internal standard) were placed in a flame-dried, serum-capped test tube and dissolved in 2 mL of dry THF. A part (0.8 mL) of the solution was withdrawn and used for calibration in the GLC analysis. To the rest of the solution was added 1 mL of the ylide solution (0.1 mmol) by means of a hypodermic syringe at 0.0 °C, and the resulting solution was allowed to react for 1 h. The solution was worked up in the usual manner and subjected to GLC analysis (1-m glass column packed with 3% PEG-HT). The relative intensity of the ketones to the internal standard was used to determine the fraction of reaction, f, and the rate ratio was calculated according to the equation

$$k_A/k_B = \log(1 - f_A)/\log(1 - f_B)$$

Carbon-14 KIE Determination. A THF solution of benzophenone-*carbonyl*-^{14}C (0.4 M, 20 mL) containing dibenzyl ether (internal standard) was divided into six parts and transferred with a stainless steel needle into flame-dried test tubes capped with rubbed septa. To these solutions were added preset amounts of ylide solution (1.0 M); the molar ratio of ylide to ketone was in the range 0.2–0.7. The solutions were allowed to react for 1 h at 0 °C and worked up as usual, and then the fractions of reaction were determined by GLC. The unreacted benzophenone was recovered from the reaction mixture and purified by repeated recrystallization from hexane. Radioactivities were measured by a liquid scintillation counter (Beckman LS 9000) as reported previously.[11] KIE was calculated by using an equation of Tong and Yankwich.[12] The results are listed in Table I.

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Force-Field Modeling of the Stereoselective Michael Additions of an Optically Active Amine and Its Lithium Amide to Acrylates

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One of us recently reported the asymmetric Michael additions of chiral amine 1 and the corresponding lithium amide to methyl crotonate.[2a] Thermal addition of amine
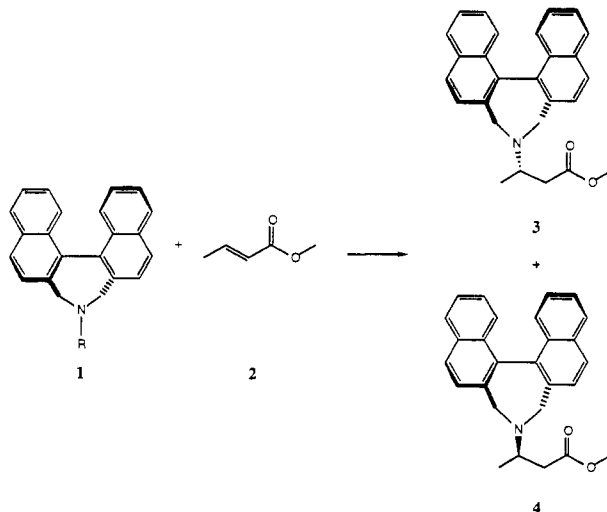
1 (R = H) gave a 61% diastereomeric excess (de) of **3** as the kinetic product, with slow equilibration to a 1:1 mixture of **3** and **4**. The corresponding lithium amide, 1 (R = Li), however, gave the opposite diastereomer, **4**, with very high selectivity (97–98% de). In order to understand the origins of these stereoselectivities, we sought a relatively accurate three-dimensional model of the respective transition states for these reactions. We have had some success in adapting Allinger's MM2[3] for this purpose[4] and undertook a similar investigation here. Since only limited experimental data were available, we could not develop transition-state parameters in a systematic manner. Our approach was to develop a reasonable model and to test it against the available data. We set out to create a force field that could help rationalize the origin of these phenomena and provide a method of prediction for related cases.[2b]

Method of Calculation

Allinger's MM2 force field[3] was used for this study. Standard parameters were used whenever possible, but some new parameters had to be introduced for these calculations. The original force field does not have parameters for two sp^2-hybridized carbons that are formally singly bonded, such as present in the binaphthyl moiety

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